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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/629,895	07/30/2003	John J. Rossi	1954-413	8585
6449 7590 06/02/2008 ROTHWELL, FIGG, ERNST & MANBECK, P.C. 1425 K STREET, N.W. SUITE 800 WASHINGTON, DC 20005				
EXAMINER WHITEMAN, BRIAN A				
ART UNIT 1635		PAPER NUMBER		
NOTIFICATION DATE 06/02/2008		DELIVERY MODE ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary

Application No.

10/629,895

Applicant(s)

ROSSI ET AL.

Examiner

Brian Whiteman

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2/29/08.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3, 5, 6 and 11-16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5, 6 and 11-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-8508)
Paper No(s)/Mail Date _____

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 2/29/08 has been entered.

Election/Restrictions

The election/restriction is moot, in view of the cancellation of claims 7-10.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "from about 4 to about 9 bases" in claim 5 is a relative term which renders the claim indefinite. The term "from about 4 to about 9 bases" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The

metes and bounds of the term 'from about 4' is not defined because is the term limited to from 4 or about 4. The specification does not define the limitation. See MPEP 2173.05(b) Section A.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 11, 12, 13 and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Agami et al. (US 7,241,618). Agami et al. teach a cell comprising a polynucleotide comprising an adenovirus VA1 promoter operably linked to a region encoding a siRNA (column 50). Agami et al. teach that siRNA is a substrate for mammalian Dicer (columns 1-3). Agami et al. teach that the siRNA can be shRNA (columns 10-13, 17, 18, 50, and 51 and Figures 8 and 10).

Applicant's arguments with respect to claims 1, 11, 12, and 13 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Agami et al. (US 7,241,618) or Polo et al. (US 6,329,201) taken with either Yu (AH) and Ambros (Cell, 2001, 107:823-6).

Polo teaches making and using an expression cassette comprising an adenoviral VA1 promoter operably linked to an antisense molecule (column 30). However, Polo does not specifically teach using RNAi in the vector, wherein the RNAi is a substrate for a mammalian Dicer and the RNAi is selected from either shRNA or precursor miRNA.

Agami et al. teach making and using an expression cassette comprising an adenoviral VA1 promoter operably linked to an siRNA molecule, wherein the siRNA molecule can be shRNA (columns 50-51 and Figures 8 and 10). Agami et al. teach that siRNA is a substrate for mammalian Dicer (columns 1-3). However, Agami does not specifically teach using RNAi in the vector, wherein the RNAi is precursor miRNA.

Furthermore, at the time the invention was made, Yu teaches an RNA polymerase III vector comprising shRNA can inhibit expression in mammalian cells. Also microRNA was well known to one of ordinary skill in the art as exemplified by Ambros (pages 823-826). Ambros teaches, "Animal genomes contain an abundance of small genes that produce regulatory RNAs of about 22 nucleotides in length (abstract)." "These microRNAs are diverse in sequence and expression patterns, and are evolutionary widespread, suggesting they may participate in a wide range of genetic regulatory pathways (abstract)."

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of either Agami or Polo taken with either Yu or Ambros, namely to produce an in vitro cell comprising the expression vector comprising an adenoviral VA1 promoter operatively linked to a construct comprising RNAi. One of ordinary skill in the art would have been motivated to combine the teaching to study a gene function in a mammalian cell in vitro.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Polo taken with Yu, namely to produce an RNA polymerase III vector comprising shRNA. One of ordinary skill in the art would have been motivated to combine the teaching as an economic alternative to chemical synthesis of siRNA.

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“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” See *KSR v. Teleflex*, 550 U.S. ___, 127 S. Ct. 1727 (2007).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of either Agami or Polo taken with Ambros, namely to produce the vector encoding microRNA. One of ordinary skill in the art would have been motivated to combine the teaching to study a gene regulatory pathway in cells in vitro. See *KSR v. Teleflex*.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

NOTE: It appears the claimed invention is directed to the expression vector and not shRNA or precursor miRNA because the instant specification generically discloses shRNA or precursor miRNA (or shRNA and precursor miRNA known in the prior art) and does not claim any novel shRNA.

Applicant's arguments with respect to claims 1 and 11-16 have been considered but are moot in view of the new ground(s) of rejection.

Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Agami or Polo taken with either Yu or Ambros as applied to claims 1 and 11-16 above, and further in view of Doglio et al. (US 5,837,503).

Agami, Polo, Yu or Ambros do not specifically teach the structural limitations of the VA1 promoter set forth in claim 2.

However, at the time the invention was made, Doglio et al. teach an expression cassette comprising a DNA oligonucleotide has been inserted between or outside the boxes A and B constituting the promoter of said VA gene (columns 19-22).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of either Agami or Polo taken with Yu and Ambros taken with Doglio, namely to produce an expression cassette comprising an adenoviral VA promoter, wherein an RNAi molecule is contained within a non-essential stem region of the promoter. One of ordinary skill in the art would have been motivated to combine the teaching to avoid reducing the activity of the promoter. See KSR v. Teleflex.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 1-3, 5, and 6 have been considered but are moot in view of the new ground(s) of rejection.

Claims 1, 2, and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Agami or Polo taken with either Yu or Ambros and Doglio et al. as applied to claims 1, 2, 5, and 6 above, and in further view of Cagnon et al. (AD).

Agami, Polo, Yu or Ambros taken with Doglio do not specifically teach the structural limitations of the VA1 promoter set forth in claim 3.

However, at the time the invention was made, Cagnon teaches inserting an RNAi molecule into a VA 1 expression cassette using a filled-in NotI site that was ligated into the BstEII cleaved, filled in vector (page 252).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Agami or Polo taken with Yu, Ambros and Doglio in further view of Cagnon, namely to produce the expression cassette wherein the non-essential stem region contains a BstEII site. One of ordinary skill in the art would have been motivated to combine the teaching to clone the siRNA into the VA1 promoter of the expression cassette since the restriction site is found in an adenoviral VA1 promoter. See KSR v. Teleflex.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Agami or Polo taken with either Yu or Ambros as applied to claims 1 and 11-16 above, and further in view of Lorens (US 20040005593).

However, at the time the invention was made, Lorens teaches an RNAi molecule having a loop containing at least 6 nucleotide bases (page 7).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of either Agami or Polo taken with either Yu or Ambros in further view of Lorens, namely to produce an expression cassette comprising an adenoviral VA promoter, wherein an RNAi molecule comprises a loop containing about 8 nucleotide bases. One of ordinary skill in the art would have been motivated to combine the teaching to increase the inhibition by using a common structure in a shRNA or precursor miRNA molecule to make the expression cassette. See KSR v. Teleflex.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 11-16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 7-9 of U.S. Patent No. US 6,995,258 taken with Frey et al. (Abstracts of General Meeting of the American Society for Microbiology 1992, 92, 225, H-254) in view of Zeng et al. Mol. Cell, 9, 1327-33, 2002. Claims 1 and 7-9 of ‘258 recite an expression cassette comprising a coding sequence for an RNA molecule an RNA pol III promoter sequence. Claim 9 recites a cell comprising the RNA molecule. One of ordinary skill in the art would understand that to express the RNA molecule in a cell the RNA pol III promoter

would have to be operably linked to the RNA molecule. However, the claims from '258 do not specifically teach using a VA1 promoter as the RNA pol III promoter to express RNAi, wherein the RNAi is selected from shRNA or precursor miRNA.

However, at the time the invention was made, Frey teaches use of an adenovirus VA1 promoter in engineering antisense RNA. The ordinary skill artisan understands that a VA1 promoter is an RNA pol III promoter.

In addition, at the time the invention was made, Zeng teaches that natural and designed microRNAs (miRNA) can inhibit the expression of mRNAs expressed in human cells (page 1327).

Furthermore, at the time the invention was made, Yu teaches an RNA polymerase III vector comprising shRNA can inhibit expression in mammalian cells.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the claims of '258 taken with Frey in further view of either Zeng or Yu, namely to produce an expression cassette comprising an RNAi molecule operably linked to a VA1 promoter, wherein the RNAi is selected from either shRNA or precursor miRNA. One of ordinary skill in the art would have been motivated to combine the teaching to improve the stability of the RNA molecule.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the claims of '258 taken with Frey in further view of either Zeng or Yu, namely to produce a mammalian cell comprising the expression cassette comprising an RNAi molecule operably linked to a VA1 promoter, wherein the RNAi molecule is selected from either precursor miRNA or shRNA. One of ordinary skill in the art would have

been motivated to combine the teaching to the study the delivery of the siRNA to the nucleolus of the cell.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 1 and 10-11 have been considered but are moot in view of the new ground(s) of rejection.

Claims 1, 5, and 6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 7-9 of U.S. Patent No. US 6,995,258 taken with Frey et al. (Abstracts of General Meeting of the American Society for Microbiology 1992, 92, 225, H-254) in view of Zeng et al. Mol. Cell, 9, 1327-33, 2002. Claims 1 and 7-9 of '258 recite an expression cassette comprising a coding sequence for an RNA molecule an RNA pol III promoter sequence. Claim 9 recites a cell comprising the RNA molecule. One of ordinary skill in the art would understand that to express the RNA molecule in a cell the RNA pol III promoter would have to be operably linked to the RNA molecule. However, the claims from '258 do not specifically teach using a VA1 promoter as the RNA pol III promoter to express RNAi, wherein the RNAi is selected from shRNA or precursor miRNA.

However, at the time the invention was made, Lorens teaches an RNAi molecule having a loop containing at least 6 nucleotide bases (page 7).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of claims of '258 taken with either Frey or Yu in further view of Lorens, namely to produce an expression cassette comprising an adenoviral

VA promoter, wherein an RNAi molecule comprises a loop containing about 8 nucleotide bases. One of ordinary skill in the art would have been motivated to combine the teaching to increase the inhibition by using a common structure in a shRNA or precursor miRNA molecule to make the expression cassette. See KSR v. Teleflex.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 2, and 3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 7-9 of U.S. Patent No. US 6,995,258 taken with Frey et al. (Abstracts of General Meeting of the American Society for Microbiology 1992, 92, 225, H-254) in view of Zeng et al. Mol. Cell, 9, 1327-33, 2002. Claims 1 and 7-9 of '258 recite an expression cassette comprising a coding sequence for an RNA molecule an RNA pol III promoter sequence. Claim 9 recites a cell comprising the RNA molecule. One of ordinary skill in the art would understand that to express the RNA molecule in a cell the RNA pol III promoter would have to be operably linked to the RNA molecule. However, the claims from '258 do not specifically teach using a VA1 promoter as the RNA pol III promoter to express RNAi, wherein the RNAi is selected from shRNA or precursor miRNA.

However, at the time the invention was made, Cagnon teaches inserting an RNAi molecule into a VA 1 expression cassette using a filled-in NotI site that was ligated into the BstEII cleaved, filled in vector (page 252).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of claims from '258 taken with either Yu or

Frey in further view of Cagnon, namely to produce the expression cassette wherein the non-essential stem region contains a BstEII site. One of ordinary skill in the art would have been motivated to combine the teaching to clone the siRNA into the VA1 promoter of the expression cassette since the restriction site is found in an adenoviral VA1 promoter. See KSR v. Teleflex.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number 571-272-0764. The examiner can normally be reached on from 6:30 to 4:00 (Eastern Standard Time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Brian Whiteman/

Primary Examiner, Art Unit 1635